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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,647	07/31/2006	Rosanne M Crooke	ISPH-0595USA	5096

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	
MAIL DATE	**DELIVERY MODE**
11/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,647	CROOKE ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6,8-11,17,50 and 52-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 6, 8-11, 17, 50, and 52-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 8/14/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 5/14/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant has added claim 67. Therefore, claims 1, 3, 6, 8-11, 17, 50 and 52-67 are pending in the application.

Applicant's arguments and/or amendments filed 8/14/07, with respect to the rejection(s) of claim(s) under 35 USC 112, 2nd paragraph and double patenting have been fully considered and are persuasive. Therefore, the rejections have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made as explained below.

Priority

As explained in the office action mailed on 5/14/07, applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application No. 60/475,402 and Application No. 10/684,440, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The applications do not teach antisense compounds that are targeted specifically to the range of nucleotides "12380-13493" of instant SEQ ID NO: 4 and do not teach the sequence of instant SEQ ID NO: 87.

Therefore, the instant claims are accorded an effective filing date of 6/2/04, the filing date of PCT/US04/14540.

Claim Objections

Claims 52 and 53 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Response to Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Cai et al. (WO 2004/108916 A1), for the reasons of record as set forth in the office action mailed on 5/14/07. It is noted that the rejection of record under 35 U.S.C. 102(e) is applied herein as a rejection under 35 U.S.C. 102(b), in view of the fact that the instantly rejected claims are accorded an effective filing date of 7/31/06 in view of the new matter rejection below.

Applicant asserts that Cai et al. cannot anticipate claim 1 and therefore does not anticipate claims 3 and 17 based on the fact that the oligonucleotide of Cai et al. is 26 nucleotides long and is 92.3% complementary to instant SEQ ID NO: 4.

As instantly recited, the antisense compound is required to be at least 94% complementary to "a portion" of nucleotides 12380-13493 of instant SEQ ID NO: 4. The antisense oligonucleotide that is a single stranded primer of Cai et al. is 100% complementary to a portion of nucleotides 12380-13493 of SEQ ID NO: 4, as instantly recited.

Specifically, the antisense oligonucleotide of Cai et al. is 26 nucleobases in length and is 100% complementary to a portion of nucleotides 12380-13493

(nucleotides 2-26 of SEQ ID NO: 6 of Cai et al. are 96% complementary to nucleotides 12805-12829 of instant SEQ ID NO: 4; nucleotides 2-11 of Cai et al. are 100% complementary to a portion of the instant sequence; and nucleotides 13-26 of Cai et al. are 100% complementary to a portion of the instant sequence).

Although applicant asserts that each nucleotide of the sequence taught by Cai et al. should be considered in the calculation, this is not required by the instant claim language. The instant claims require for the antisense compound to be at least 94% complementary to any portion of any size of nucleotides 12380-13493 of instant SEQ ID NO: 4 and is therefore inconsistent with applicant's argument that every nucleotide should be involved in the calculation.

Since the oligonucleotide of Cai et al. meets the structural limitations of the instant claims, the antisense compound necessarily meets the instant limitation of being "targeted to a nucleic acid molecule encoding apolipoprotein(a)", as instantly claimed.

Therefore, the instant invention is anticipated by Cai et al.

Response to Claim Rejections - 35 USC § 103

Claims 1, 3, 6, 8-11, 17, 54-60 and 62-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruoy et al. (WO 99/35241), in view of Morishita et al. (Circulation, 1998, 98, pages 1898-1904) and Baracchini et al. (U.S. patent 5,801,154), for the reasons of record as set forth in the office action mailed on 5/14/07.

It is noted that newly added claim 67 is included in the instant rejection, as the chimeric configuration is considered obvious in view of Baracchini et al., as further explained below.

Applicant asserts that the examiner has not identified an explicit reason to combine the elements of the prior art in the manner defined by the claims at issue. Contrary to applicant's assertion, as explained in the office action mailed on 5/14/07, one would have been motivated to target the coding region of apolipoprotein(a) with the antisense oligonucleotides of Ruoy et al. because Morishita et al. teach targeting ribozymes to the coding region of apolipoprotein(a) for inhibition of target gene expression and Baracchini et al. teach that the coding region is a preferable target region for antisense oligonucleotides in general. Due to the size and accessibility of the coding region, there would be a reasonable expectation of success to target an antisense oligonucleotide to this region, as demonstrated by Baracchini et al.

Applicant asserts that Morishita et al. teach away from the instant invention and that Morishita et al. teach that antisense compounds should not be used to modulate apolipoprotein(a) expression. Applicant's interpretation of the Morishita et al. reference is considered erroneous. Morishita et al. does not teach that antisense compounds should not be used to modulate apolipoprotein(a) expression. Morishita et al. teaches that both antisense oligonucleotides and ribozymes are approaches to combat disease processes and that Morishita et al. chose to use a ribozyme because it appears to be very difficult to use the antisense strategy to decrease apo(a) separate from plasminogen because the structure of the apo(a) gene has a very high degree of

homology to the plasminogen gene (see paragraph bridging pages 1898 and 1899 of Morishita et al.). Therefore, Morishita et al. does not question whether or not antisense oligonucleotides should be used to target apo(a), but rather only brings to question whether antisense oligonucleotides are preferable to ribozymes when specifically attempting to target apo(a) and not plasminogen, which is not an element of the instant claims.

Given that Ruoy et al. teach antisense nucleic acids that are capable of specifically hybridizing with a nucleic acid encoding apolipoprotein(a) and down regulating gene expression, combined with the known preferential properties of antisense oligonucleotides as well as targeting the coding region, as taught by Baracchini et al., one would certainly be motivated and have a reasonable expectation of success in targeting an antisense oligonucleotide to the coding region of apo(a). Furthermore, since Morishita et al. teach targeting the apo(a) coding region with ribozymes, which are also sequence specific inhibitors of target gene expression, one would have been motivated to target the coding region with an antisense oligonucleotide as well. Morishita et al. is evidence that it was known in the art at the time the invention was made to target the coding region of apolipoprotein(a).

Applicant further asserts that Morishita et al. teaches away from the instant invention because Morishita et al. utilized a DNA oligonucleotide without ribozyme activity as a negative control, wherein the DNA oligonucleotide did not inhibit apo(a) expression. The basis of applicant's assertion is unclear because scrambled controls are routinely utilized in the art, regardless of whether the control is an antisense

oligonucleotide or ribozyme. The DNA oligonucleotide referred to by applicant is disclosed as a sequence specifically chosen as a negative control because it is a mismatched sequence. This is not evidence of any activity of antisense oligonucleotides that match that target sequence. Morishita et al. utilized a mismatched ribozyme as well that did not result in activity (see page 1899, column 1). Both the mismatched ribozyme and DNA oligonucleotide were specifically designed to be negative controls.

Baracchini et al. teach that typically chimeric oligonucleotides are "gapped" oligonucleotides (or "gapmers") in which a region of deoxynucleotides (the "gap"), preferably containing at least four contiguous deoxynucleotides, is flanked by regions of modified nucleotides, preferably 2'-sugar modified nucleotides. In a preferred embodiment, the flanking regions (or "wings") contain 2'-alkoxy or 2'alkoxyalkoxy modifications, more preferably 2'-methoxyethoxy. In preferred embodiments the backbone may be phosphorothioate throughout or may be phosphodiester in the "wings" and phosphorothioate in the "gap". In other preferred embodiments, chimeric oligonucleotides may be "winged" oligonucleotides (or "wingmers" or hemichimeras) in which there is a deoxy "gap", preferably at least 4 contiguous deoxynucleotides, flanked on either the 5' or the 3' side by a region of modified nucleotides. Again, the flanking region (or "wing") preferably contains 2'-alkoxy or 2'alkoxyalkoxy modifications, more preferably 2'-methoxyethoxy and the backbone may be phosphorothioate throughout or may be phosphodiester in the "wing" and phosphorothioate in the "gap". Other configurations of chimeric oligonucleotide are also comprehended by this invention.

These may involve other modifications of the sugar, base or backbone, preferably in the oligonucleotide wing(s).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to make an antisense oligonucleotide to apolipoprotein(a) as taught by Ruoy et al. with the chemical modifications taught by Baracchini et al. targeted to the coding region, as taught by Morishita et al. and Baracchini et al.

One would have been motivated to target the coding region of apolipoprotein(a) with the antisense oligonucleotides of Ruoy et al. because Morishita et al. teach targeting ribozymes to the coding region of apolipoprotein(a) for inhibition of target gene expression and Baracchini et al. teach that the coding region is a preferable target region for antisense oligonucleotides in general. Due to the size and accessibility of the coding region, there would be a reasonable expectation of success to target an antisense oligonucleotide to this region, as demonstrated by Baracchini et al.

One would have been motivated to incorporate a chimeric configuration, 2'-O-methoxyethyl sugar moieties, phosphorothioate linkages, or 5-methylcytosine modifications into the antisense oligonucleotides of Ruoy et al. because Baracchini et al. teaches each of these elements and teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases.

One would have a reasonable expectation of success for each of the instant modifications to benefit the antisense oligonucleotides of Ruoy et al. because the

chemistry was well known, as demonstrated by Baracchini et al. and Morishita et al. Ruoy et al. teaches that it is beneficial to modify antisense oligonucleotides, whereas Baracchini et al. and Morishita et al. teach specific chemical modifications for the same benefits.

Therefore, the invention of the above claims would have been obvious, as a whole, at the time the instant invention was made.

Claims 1, 3, 6, 8-11, 17, and 54-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruoy et al. (WO 99/35241), in view of Morishita et al. (Circulation, 1998, 98, pages 1898-1904) and Baracchini et al. (U.S. patent 5,801,154), as explained in the 35 U.S.C. 103(a) rejection above, further in view of Ramasamy (US 6,525,191 B1), for the reasons of record as set forth in the office action mailed on 5/14/07.

It is noted that newly added claim 67 is included in the instant rejection, as the chimeric configuration is considered obvious in view of Baracchini et al.

Applicant's arguments have been addressed in the rejection under 35 U.S.C. 103(a), above.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 6, 8-11, 17, 50, and 52-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

Instant claim 1 recites "at least 94% complementary to a portion of nucleotides 12380-13493 as set forth in SEQ ID NO: 4". Claim 50 recites "at least 90% complementary to a portion of nucleotides 12380-13493 as set forth in SEQ ID NO: 4". Claims 3, 6, 8-11, 17, and 52-56 are rejected because they depend from claim 1 or 50.

The specification discloses that complementarity between the oligomeric compound and target is about 94% (see page 10). However, the instant specification does not disclose a limitation wherein the compound is at least 90% or 94% complementary to a portion of nucleotides 12380-13493 as set forth in SEQ ID NO: 4. The instant specification discloses that the antisense compounds target a portion of nucleotides 1-2480 as set forth in SEQ ID NO: 4. The only other context that the instant specification discloses targeting a "portion", as instantly recited, is targeting an 8-nucleobase portion of the regions disclosed on page 19 of the instant specification. Therefore, the instant specification does not support compounds that are at least 90% or 94% complementary to a portion of nucleotides 12380-13493 as set forth in SEQ ID NO: 4, which encompasses portions that are as little as 2 nucleotides, for example.

There is no support for these claim limitations in the claimed priority documents. Therefore, the effective filing date of claims 1, 3, 6, 8-11, 17, 50, and 52-56 is considered, for purposes of prior art, to be 7/31/06, which is the filing date of the instant application.

A review of the specification does not reveal support for where the instant claim amendments are found. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each of the above mentioned claim limitations.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 17, and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Mittman (US 2003/0104410 A1).

The instant claims are directed to an antisense compound 15 to 30 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein(a), wherein said compound is at least 94% complementary to a portion of nucleotides 12380-13493 as set forth in SEQ ID NO: 4, wherein the compound comprises an antisense oligonucleotide and is single-stranded. The claims are further directed to an antisense compound 15 to 30 nucleobases in length targeted to a nucleic acid molecule encoding

apolipoprotein(a), wherein said compound is at least 90% complementary to a portion of nucleotides 12380-13493 as set forth in SEQ ID NO: 4 and wherein the compound comprises at least 8 contiguous nucleobases of SEQ ID NO: 87.

Mittman teaches an antisense oligonucleotide that is 25 nucleotides in length, wherein the antisense compound comprises 13 contiguous nucleotides of instant SEQ ID NO: 87 and therefore is 100% complementary to a portion of nucleotides 12380-13493 of instant SEQ ID NO: 4 because SEQ ID NO: 87 is a sequence within SEQ ID NO: 4 (see SEQ ID NO: 427 of Mittman et al; search result #10 in the search labeled "20070502_095112_us-10-559-647-87.szlm30.rng" in SCORE). It is noted that the instant claims require that the antisense compound is at least 90% complementary to any portion of any length of nucleotides 12380-13493 of instant SEQ ID NO: 4 and does not require that the full length antisense compound have such complementarity. Instant claims 54 and 55, for example, are excluded from the instant rejection because they necessitate that the antisense compound is at least 95% or 100%, respectively, complementary to instant SEQ ID NO: 4, whereas the instantly rejected claims only require complementarity to any portion of any size of nucleotides 12380-13493 of instant SEQ ID NO: 4.

Since the oligonucleotide of Mittman meets the structural limitations of the instant claims, the antisense compound necessarily meets the instant limitation of being "targeted to a nucleic acid molecule encoding apolipoprotein(a)", as instantly claimed.

Therefore, the instant invention is anticipated by Mittman.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755. The examiner can normally be reached on Monday-Thursday 6:30 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amy H. Bowman
Examiner
Art Unit 1635

AHB

/J. E. Angell/
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